CASE REPORT

# T wave alternans after sotalol: evidence for increased sensitivity to sotalol after conversion from atrial fibrillation to sinus rhythm

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**Abstract**

**A 64 year old woman with an 11 year history of paroxysmal atrial fibrillation presented to the emergency room because of palpitations that had started two weeks previously. She had used sotalol 80 mg once daily for three years without any episodes of proarrhythmia or other adverse effects. However, she developed pronounced T wave alternans with giant inverted T waves and excessive QT prolongation following sotalol administration one day after conversion from atrial fibrillation to sinus rhythm. This case demonstrates bizarre T wave changes, T wave alternans, and extreme QT prolongation following sotalol administration shortly after conversion from atrial fibrillation to sinus rhythm. In this situation, sotalol administration may be proarrhythmic, because it enhances repolarisation inhomogeneities based on a spatially inhomogeneous distribution of repolarisation controlling ion channels to induce repolarisation abnormalities that may lead to torsade de pointes.**
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Keywords: T wave alternans; long QT syndrome; torsade de pointes; sotalol; atrial fibrillation

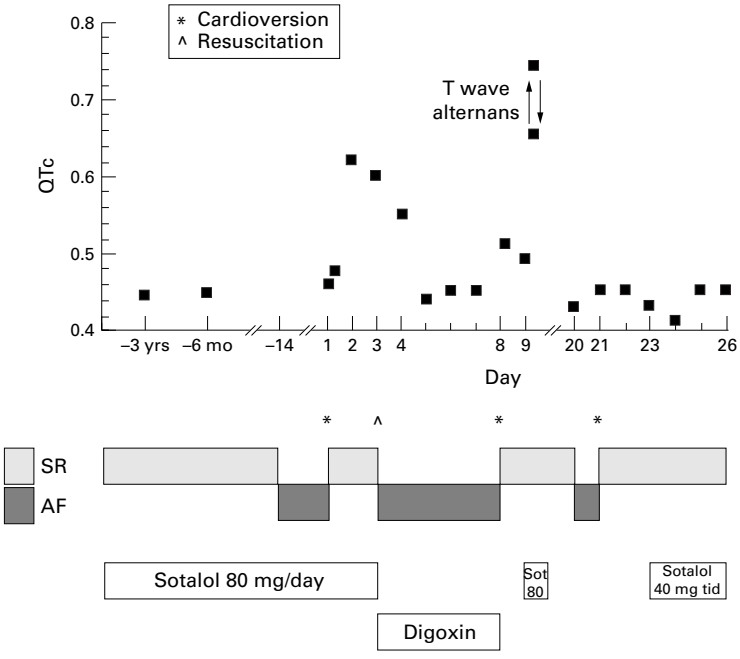


*Figure 1 Clinical events and ECG features. Abscissa is time scale whereby day 1 represents the day of the first presentation to the emergency room. Ordinate shows QTc duration. −3 yrs, 3 years before day 1; −6 mo, 6 months before day 1; SR, sinus rhythm; AF, atrial fibrillation; sot 80, single oral dose of 80 mg sotalol.*

The ECG T wave reflects cardiac repolarisation. Its broad inscription results from the temporal inhomogeneity with which repolarisation proceeds through the heart. T wave changes, including T wave inversion and T wave alternans, have been subdivided into primary and secondary forms. The latter results from a changed repolarisation sequence following an altered activation sequence (such as bundle branch block), whereas the former are caused by other factors.[1] T wave alternans is a characteristic feature of congenital long QT syndrome (LQTS)[2 3]: it is associated with the excessive QT prolongation required for torsade de pointes[4] and often precedes torsade de pointes.[5] T wave alternans also occurs in LQTS induced by drugs that prolong the action potential.[6]

In patients receiving quinidine for atrial fibrillation, torsade de pointes occurs most often shortly after conversion from atrial fibrillation to sinus rhythm.[7] The mechanism underlying this finding is unknown. It may be caused by delayed adaptation of repolarisation to the sudden change of heart rate,[8] but an increased sensitivity to drugs that prolong the action potential in the period shortly following conversion to sinus rhythm may also play an important role.[9]

We describe a patient who was using sotalol for paroxysmal atrial fibrillation for three years without proarrhythmic effects or significant T wave changes, but she developed pronounced T wave alternans with giant inverted T waves and excessive QT prolongation following sotalol administration one day after conversion from atrial fibrillation to sinus rhythm. Figure 1 summarises the clinical events and ECG features of this case.

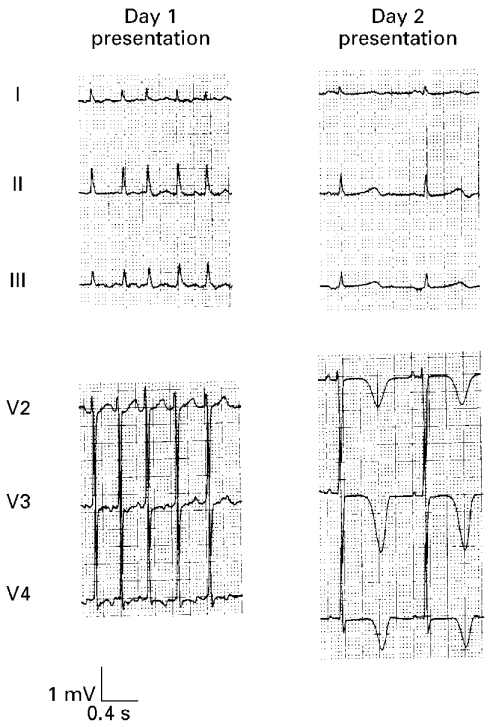


*Figure 2 Left, ECG at presentation on day 1; Right, ECG at presentation on day 2.*

## Case report

A 64 year old woman with an 11 year history of paroxysmal atrial fibrillation presented to our emergency room because of palpitations that had started two weeks previously. She had used sotalol 80 mg once daily (and acenocoumarol) for three years without any episodes of proarrhythmia or other adverse effects. ECGs during sinus rhythm six months and three years before presentation showed a QT interval of 0.44 seconds and a rate corrected (Bazett) QTc of 0.45; ST segments and T waves were normal. The voltages in the precordial leads met the criteria for left ventricular hypertrophy; however, this was probably due to her slender build as echocardiography showed no cardiac hypertrophy. There was no history of coronary artery disease or angina pectoris at presentation or at any time during admission. ECG at presentation revealed atrial fibrillation with an average ventricular rate of 160 beats/min (QT 0.28 seconds, QTc 0.46). The T waves were flattened in most leads (fig 2, left panel). Physical examination and laboratory tests were normal (height 176 cm, weight 48 kg, average blood pressure 150/70 mm Hg, $K^+$ 3.9 mmol/l, creatinine 44 μmol/l, INR 3.2). Echocardiography showed a mildly dilated, not hypertrophic, left ventricle with mildly impaired left ventricular function without wall motion abnormalities. Both atria were mildly dilated and there was no thrombus in the left atrium. To achieve sinus rhythm we infused 100 mg flecainide. The resulting ECG showed sinus rhythm of 72 beats/min with negative T waves in $V_2$ through $V_5$ (QT 0.42 seconds, QTc 0.47). The patient was discharged and instructed to continue taking sotalol and acenocoumarol.

The next day (day 2) she returned to the emergency room because she had suffered a transient episode of aphasia and right sided hemiparesis the night before. On presentation, her neurological dysfunctions had almost completely disappeared. The ECG showed an atrial rhythm of 60 beats/min with deeper (compared to the ECG at discharge on day 1, not shown) negative T waves in $V_2$ through $V_4$, with a QT and QTc duration of 0.62 and U waves in all leads including the limb leads (fig 2, right panel). Although computed tomography of the brain showed no haematoma or cerebrovascular accident, she was admitted to the neurology ward for observation.

The next morning (day 3), two hours after taking sotalol, she suddenly experienced lightheadedness, which was promptly followed by syncope. No cardiac rhythm monitoring was present, but physical examination showed severe hypotension (systolic blood pressure 60 mm Hg) and cyanosis. There were no signs of epilepsy. Chest compressions quickly restored blood pressure and consciousness, and the patient was referred to the coronary care unit. On admission there, the ECG showed atrial fibrillation with an average ventricular rate of 150 beats/min and positive TU waves in $V_2$ through $V_5$. The QT was 0.36 seconds and the QTc 0.60. Average blood pressure was 110/80 mm Hg. Sotalol was stopped and digoxin was administered to control ventricular rate. The next day (day 4) the T waves in $V_2$ through $V_4$ had become deeply negative again. Over the next days atrial fibrillation persisted at an average ventricular rate of 80 beats/min. No ventricular tachyarrhythmias occurred and the neurological signs completely disappeared. The QT and QTc intervals gradually normalised and the T waves flattened in all leads. On day 8, electrical cardioversion restored sinus rhythm of 55 beats/min with a QT interval of 0.52 seconds and a QTc of 0.51. The deep negative T waves in $V_2$ through $V_5$ reappeared. Digoxin was stopped. The next day (day 9), we administered a challenge oral dose of 80 mg sotalol. The QT and QTc immediately before sotalol administration were 0.50 seconds and 0.49, respectively (fig 3, left panel). Within 90 minutes of sotalol administration there were giant negative T waves with T wave alternans in $V_2$ through $V_5$ and prominent U waves in alternate beats in all leads. QT and QTc intervals were prolonged: in $V_3$, QT alternated between 0.82 and 0.72 seconds, while QTc alternated between 0.74 and 0.65 (fig 3, right panel). This prompted us to stop sotalol.

The next day (day 10), T wave alternans was no longer present and over the next few days the T waves in the precordial leads gradually became positive. On day 20, atrial fibrillation recurred with an average ventricular rate of 100 beats/min and positive T waves in all leads. Electrical cardioversion (day 21) restored sinus rhythm without changing the T wave morphology. Two days later (day 23) sotalol (40 mg tid) was readministered to prevent recurrence of atrial fibrillation. Within three days, the T waves in $V_2$ through $V_3$ became negative and prominent U waves occurred in the precordial

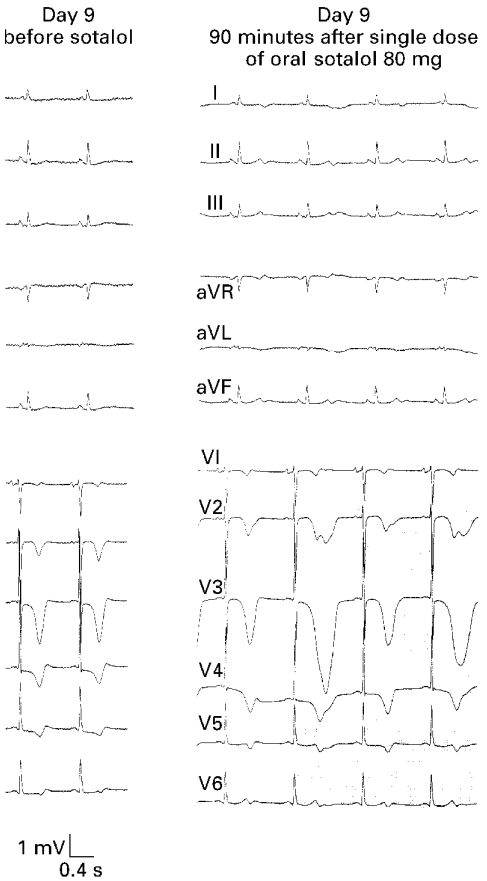


*Figure 3 Left, ECG immediately before single oral dose of sotalol 80 mg on day 9; Right, ECG 90 minutes after single oral dose of sotalol 80 mg on day 9.*

leads; QT and QTc duration were not excessively prolonged at 0.50 seconds and 0.45, respectively. We stopped sotalol and started flecainide (50 mg bid) after which no atrial fibrillation recurred.

## Discussion

This case demonstrates pronounced T wave instability. Its most striking features are giant negative T waves with T wave alternans and extreme QT prolongation following sotalol administration one day after conversion from atrial fibrillation to sinus rhythm (day 9, fig 3). This extends the findings from reports that showed increased sensitivity to quinidine, another action potential prolonging drug, causing excessive QT prolongation and torsade de pointes shortly after conversion from atrial fibrillation to sinus rhythm.[7] This propensity for torsade de pointes may be associated with the T wave changes described in our case. Although we have no ECG of the syncope episode on the neurology ward, it was probably caused by torsade de pointes, considering the QT prolongation and the deep negative T waves and U waves on admission. Also, the intracerebral pathology (albeit without apparent substrate) may have facilitated torsade de pointes,[10] although her neurological symptoms had been brief and had almost completely resolved on admission to the neurology ward.

### T WAVE CHANGES AFTER SUDDEN HEART RATE SLOWING AND THE ROLE OF $I_{Kr}$ BLOCKADE

T waves result from repolarisation, which occurs with temporal inhomogeneity between the transmural layers. This is based on an inhomogeneous distribution of repolarisation controlling ion channels: the transient outward current, $I_{to}$, is present in epicardium and mid-myocardium, but not in endocardium,[11 12] while the slowly activating/deactivating component of the delayed rectifier current, $I_{Ks}$, is smaller in the mid-myocardium than in the other layers.[13] Also, the activity of the inward rectifier current, $I_{K1}$, differs between these layers.[14] Some conditions alter these inhomogeneities—for instance, in hypertrophic hearts, $I_{to}$ density is decreased.[15 16] In isolated tissue preparations, these inhomogeneities cause profoundly different action potential durations in the transmural layers.[12 13] Whether these differences are as large in situ is questionable, because electrotonic interactions between adjacent layers should cancel out differences.[17] Still, the inhomogeneous distribution of repolarisation controlling ion channels constitutes a substrate for alterations in the repolarisation sequence, which may translate into T wave changes. These alterations may be caused by different responses to abrupt changes of heart rate. At baseline, action potentials are shorter in the epicardium than the endocardium, partly because of the presence of $I_{to}$ in the former but not the latter. This results in the general direction of repolarisation being from epicardium to endocardium—that is, opposite to the direction of depolarisation. This translates into concordance between the T wave and its QRS complex (positive T waves in leads where the QRS complexes are positive).[18] However, action potential prolongation in response to slow heart rates is more pronounced in the epicardium (and mid-myocardium) than the endocardium.[11] This may result in a reversed direction of repolarisation and T wave inversion.[18]

Drugs that prolong the action potential may exacerbate these T wave changes by also blocking $I_{Kr}$, the rapidly activating drug sensitive component of the delayed rectifier current.[19] $I_{Kr}$ block per se should not cause repolarisation inhomogeneities because $I_{Kr}$ activity does not differ between the transmural layers.[13] However, $I_{Kr}$ block may enhance the relative roles of the remaining repolarising currents ($I_{to}$, $I_{Ks}$, and $I_{K1}$) in repolarisation and unmask the inequalities in their spatial distribution, thereby intensifying T wave changes, including T wave alternans. The effects of $I_{Kr}$ blockers may be even greater after conversion from atrial fibrillation to sinus rhythm because of reverse use dependence, whereby $I_{Kr}$ blockade increases at slow heart rates.[20] In addition, $I_{Kr}$ blockers may exert greater effects in individuals with gene defects causing QT prolongation. For instance, those who already have insufficient $I_{Kr}$ activity because of an abnormal HERG gene, which encodes for $I_{Kr}$ (LQT2 type of congenital LQTS[2]), may develop excessive T wave changes, QT prolongation, and torsade de pointes when they take $I_{Kr}$ blockers. Those

with subclinical HERG gene defects (forme fruste of LQT2 with normal QT duration at baseline) may also be prone to these effects when challenged with $I_{Kr}$ blockers.[21] A similar situation may arise in patients with subclinical forms of the LQT1 type of congenital LQTS, which is based on an abnormal KvLQT-1 gene, which encodes part of $I_{Ks}$.[22 23] We did not perform gene analysis in our patient.

## MECHANISMS OF T WAVE ALTERNANS

Different mechanisms may explain T wave alternans. T wave alternans in LQTS induced by action potential prolonging drugs may result from early afterdepolarisations (EADs) taking off in alternate beats from phase 2 or phase 3 of the action potential.[6] Intracellular $Ca^{2+}$ overload after excessive QT prolongation may cause oscillatory $Ca^{2+}$ release from the sarcoplasmic reticulum, which may induce EADs, T wave alternans, and torsade de pointes.[24] Alternatively, T wave alternans at short diastolic intervals (which occurs when QT prolongation is so great that the QT intervals encroach on the following QRS complexes) was explained as follows.[18] If the diastolic interval is shorter than a critical value, the following activation behaves as a premature beat and exhibits action potential shortening.[25] This may be based on slow deactivation of $I_{Ks}$, which results in residual repolarising current at the start of the following activation.[2] If the RR interval is constant, the ensuing diastolic interval again becomes longer than the critical value. This allows the following action potential to be of a normal duration, such that the ensuing diastolic interval is short again and another shortening–lengthening cycle of the QT interval may start.

## CONCLUSION

This case illustrates that sotalol may exert a potentially proarrhythmic effect in the period shortly after conversion from atrial fibrillation to sinus rhythm. This proarrhythmia may even occur in patients who have been taking sotalol for several years. This finding may have clinical relevance in that it lends support to the policy of initiating sotalol treatment during this situation under closely monitored conditions requiring hospital admission,[7] and it warrants a prolonged period of monitoring after cardioversion in the presence of action potential prolonging drugs.


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